UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/080,797	02/21/2002	Romulus Kimbro Brazzell	OP/4-31881A	9942

1095 7590 06/17/2003

THOMAS HOXIE
NOVARTIS, CORPORATE INTELLECTUAL PROPERTY
ONE HEALTH PLAZA 430/2
EAST HANOVER, NJ 07936-1080

EXAMINER	
ANGELL, JON E	

ART UNIT	PAPER NUMBER
1635	10

DATE MAILED: 06/17/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 10/080,797	Applicant(s) BRAZZELL ET AL.	
	Examin r J. Eric Angell	Art Unit 1635	

-- The MAILING DATE of this communication appears n the c ver sheet with the correspondence address --

Peri d for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 September 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-42* is/are pending in the application.

4a) Of the above claim(s) *4,9-16,23-26 and 42* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5-8,17-22 and 27-41* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *7,8* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. This Action is in response to the communication filed on 9/6/02, as Paper No. 9.

Election/Restrictions

2. Applicant's election without traverse of Group II, claims 1-3, 5-8, 17-22 and 27-41 as they are drawn only to a method for treating ocular neovascularization by administering a viral vector comprising an endostatin-encoding nucleic acid, in Paper No. 9 is acknowledged.

3. Claims 4, 9-16 and 23-26 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 9.

4. Claims 1-3, 5-8, 17-22 and 27-41 are examined herein to the extent that they ready upon the elected invention (a method for treating ocular neovascularization by administering a viral vector comprising an endostatin-encoding nucleic acid).

Claim Objections

5. Claims 1-5 28 and 29 are objected to because of the following informalities: It is acknowledged that the instant claims are linking claims that are very broad and encompass elected as well as non-elected subject matter. Specifically, the claims encompass methods of treating ocular neovascularization using a viral vector (the elected invention) as well as administering a polypeptide (a non-elected invention). Therefore, the instant claims are rejected to for encompassing non-elected subject matter. Appropriate correction is required.

Claim Rejections - 35 USC § 112, second paragraph

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 1-5, 28 and 29 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: the administration of the viral vector operably encoding endostatin. Without a clear indication that the method comprises administration of a viral vector operably encoding endostatin, it is unclear how the method can effect an increase in the amount of endostatin in the ocular tissues of an individual.

8. Amending claim 1 to add the step of administering a viral vector operably encoding endostatin would obviate this rejection.

Claim Rejections - 35 USC § 112, first paragraph

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 1, 3, 5-8, 17-22 and 28-41are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

11. The instant claims are drawn to a method for the treatment of ocular neovascularization comprising administering a viral vector comprising an endostatin-encoding nucleic acid. Claim 3 indicates that the endostatin encoded by the nucleic acid can be a polypeptide as set forth in SEQ ID NO: 1, or a derivative or variant thereof. It is pointed out that the derivatives and variants of SEQ ID NO: 1 encompass any possible derivative or variant of SEQ ID NO: 1 and includes sequences comprising all possible additions, deletions or substitutions. Therefore, the claims clearly encompass sequences which are not described in the specification.

The Written Description Guidelines for examination of patent applications indicates, "the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, or by disclosure of relevant, identifying characteristics, i.e. structure or other physical and/or other chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show applicant was in possession of the claimed genus." (See MPEP 2100-164)

In the instant case the claims encompass a genus comprising a huge number of different species, considering every possible sequence that is a derivative or variant of the reference sequence, including variant and derivative sequences which are not functionally active molecules. The specification indicates that sequences encoding endostatin or fragments, derivatives or analogues thereof are described in U.S. Pat. No. 5,854,205 (incorporated by reference). The specification discloses endostatin that is 18kDa-20kDa in size and includes active precursor forms of this protein (see p. 4, lines 35). The specification also describes active fragments of endostatin which have substantially similar sequence and are capable of inhibiting

endothelial cell proliferation and includes endostatin molecules with silent mutations (p. 4, line 24-29). However, because the claims are not limited to "functionally active variants or derivatives of endostatin" as described in the specification, there is insufficient description of the genus of molecules encompassed by the claims. The disclosed description of the genus does not describe the relevant, identifying characteristics, i.e. structure or other physical and/or other chemical properties common to all members of the genus, nor have any functional characteristics coupled with a known or disclosed correlation between function and structure been identified. Therefore, the disclosure does not meet the written description requirement.

12. Claims 1, 3, 5-8, 17-22 and 28-41 are also rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

As mentioned above, the instant claims encompass sequence for which there is insufficient written description provided in the specification. Without a clear indication of the sequence encompassed by the claims one of skill in the art would not know how to make or use the claimed invention without performing an undue amount of additional experimentation in order to identify the different species of molecules encompassed by the claims.

13. Claims 1-3, 5-8, 17-22 and 27-41 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

Method 1) A method for therapeutically treating ocular neovascularization in an individual afflicted with ocular neovascularization wherein said method comprises directly administering to the eye or eyes of said individual a viral vector that operably encodes and expresses endostatin such said administration results in the amelioration of said ocular neovascularization; and,

Method 2) A method for treating choroidal neovascularization (CNV) in an individual afflicted with CNV wherein said method comprising administering to said individual a replication defective adenoviral vector that operably encodes and expresses endostatin, wherein said replication defective adenoviral vector is administered to the blood stream of said individual effected with CNV such that said administration results in the amelioration of said CNV,

does not reasonably provide enablement for the full scope of the method encompassed by the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988).

Wands states on page 1404,
"Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the

prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention

The instant claims are drawn to a method of treating ocular neovascularization by administering a viral vector encoding endostatin. Therefore the general nature of the invention is ocular gene therapy.

The breadth of the claims

The presently pending claims are very broad and encompass treating any type of ocular neovascularization by administering any type of viral vector encoding endostatin wherein said viral vector can be administered to by ant means to any location in the individuals body. Furthermore, the claims encompass prophylactic treatment (i.e. preventing) as well as therapeutic amelioration of ocular neovascularization.

The unpredictability of the art and the state of the prior art

The relevant prior art indicates that methods of gene therapy for the eye, at the time of invention was highly unpredictable. For instance, Ashton (1998, cited in IDS as reference AR) teaches,

> "The eye barriers greatly limit ocular exposure to topically and systemically applied compounds. This necessitates the administration of high does to achieve therapeutic ocular levels and the resulting high systemic exposure can then reduce the therapeutic index of otherwise promising agents." (see lines 1-5 of Abstract)

Additionally, Wright (Brit. Journ. Opthalmol. 1997, Vol. 81, No. 8, pages 620-623.) indicates a number of problems related to gene therapy for the eye. For instance, Wright teaches,

"As long term gene expression is the goal, success depends on (i) efficient uptake into the target cells, (ii) avoidance of endocytosis and lysosomal degradation, (iii) import into the

nucleus, (iv) stable retention in the nucleus, either as a circular episome (for example adenovirus) or by integration into the host genome, (v) target cell specific expression the therapeutic gene, driven by the natural promoter and enhancer elements, (vi) appropriate translation and subcellular localization of the gene product. The most difficult steps are probably (iii), (iv) and (v)." (See p. 620, first column).

Regarding the long term expression of a reporter gene in the eye using an adenoviral vector, Wright teaches, "Transgene expression declined with time because of factors such as low grade immune reaction, switch off, or loss of the episomal transgene." (See p. 621, first column). Wright also indicates that the future of gene therapy for the eye will require additional work that is not a matter of routine experimentation. Specifically, Wright teaches,

"It is difficult to predict the key ingredients required for success in retinal gene therapy. Less immunogenic vectors will certainly be helpful but one worrying possibility is that unless chromosomal integration of the introduced gene occurs, expression will be too short lived (fore example, not more than one year) to be useful. None of the currently used vectors (ABV, AAV, HSV1) integrates at an appreciable frequency , and although this can be seen as an advantage for dividing cells (less chance of oncogenic damage) it is probably a disadvantage in post-mitotic cell." (See p. 621 under "Future Developments")

As mentioned above, the claims also encompass prophylactic treatment (i.e. methods of preventing ocular neovascularization). Prophylactic methods encompass the prevention of any future occurrence of neovascularization. There are no examples presented in the instant specification or in the relevant prior art that gene therapy can be used to prevent all future occurrence of any disease for the entire life of an individual. Considering that such treatment would require the expression of a "preventative" amount of the therapeutic protein for the life of the individual and considering the teaching in the prior art that long term expression of a therapeutic molecule in eye cells is still a very challenging feat, it is highly unlikely that it would be a matter of routine experimentation to make a gene therapy construct that could be used to prevent any future occurrence of ocular neovascularization for the entire life of an individual.

Working Examples and Guidance in the Specification

The specification has working examples which disclosing: 1) a method for therapeutically treating CNV in an individual afflicted with CNV wherein said method comprises administering a replication deficient adenoviral vector operably encoding endostatin directly to the bloodstream an individual afflicted with CNV such that said administration results in the amelioration of CNV in said individual (e.g., See Example 2, p. 19-22); and 2) a method for inhibiting ocular neovascularization in an individual afflicted with ocular neovascularization wherein said method comprises directly administering to the eye of said individual a BIV vector encoding murine endostatin such that said administration results in the inhibition of ocular neovascularization in said individual (e.g., see Example 8, p. 27)

Quantity of Experimentation

Considering the breadth of the claims and the unpredictable nature of gene therapy for the eye, and the limited amount of working examples and guidance provided, it is clear that additional experimentation would be required in order to practice the claimed method to the full scope encompassed by the claims. Specifically, additional experimentation would have to be performed in order to perfect methods of gene therapy for ocular neovascularization wherein any vector encoding endostatin can be administered by any route of administration (such as systemic administration) and result in the treatment of ocular neovascularization. Furthermore, experimentation would have to be performed in order to perfect the claimed method for preventing any future occurrence of ocular neovascularization. Considering the teachings of the prior art (indicated above) it is highly unlikely that the additional experimentation is a matter of routine experimentation.

Level of the skill in the art

The level of the skill in the art is deemed to be high.

Conclusion

Considering the breadth of the claims, the high degree of unpredictability recognized in the art, the limited working examples and guidance provided (in view of the breadth of the claims); and the high degree of skill required, it is concluded that the amount of experimentation required to perform the broadly claimed invention is undue.

It is noted that amending the claims to be limited to the method described in Method 2) above would obviate this rejection.

Claim Rejections - 35 USC § 102

14. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

15. Claims 1-3, 5-9, 27, 28, 30 and 31 are rejected under 35 U.S.C. 102(b) as being anticipated by Leboulch et al. (WO 99/26480, cited as IDS reference AN).

16. Leboulch teaches a method for treating a human patient suffering from diabetic retinopathy by administering a to said patient a nucleic acid molecule which expresses endostatin wherein expression of the endostatin polypeptide in the patient inhibits angiogenesis in the vicinity of the retina (e.g., see claim 33, page 33-34). Specifically, Leboulch teaches that the gene therapy vector can be a retroviral vector, or adenoviral vector (see p. 5, lines 19-21). Furthermore, Leboulch indicates that the gene therapy vector can be administered by any method that allows the vector to reach the target cells, such as injection to the target tissue, wherein the target tissue can be the retina of the eye (e.g., see p. 11, lines 10-22; and p. 14, lines 2-14; and claim 33). Therefore, Leboulch anticipates the instant claims.

It is noted that amending the claims to the method described in Method 2) above would obviate this rejection.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to J. Eric Angell whose telephone number is (703) 605-1165. The examiner can normally be reached on M-F (8:00-4:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on (703) 308-0447. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

DAVE T. NGUYEN
PRIMARY EXAMINER

J. Eric Angell
June 16, 2003